PCT/IN04/00102

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THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Complete Specification filed on 21.4.2003 of the extract of Patent Application No.330/MAS/2003 by M/s. MATRIX LABORATORIES LTD., registered office at 1-1-151/1,IV Floor, Sairam Towers, Alexander Road,Secunderebad-500 003,Andhra pradesh, India.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 16th day of JUNE, 20034
27th day of Jyaistha, 1926 (Saka)

M.S. Venkataraman

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FORM - 2

THE PATENTS ACT, 1970

(39 OF 1970)

COMPLETE SPECIFICATION

(See Section 10)

1.TITLE OF INVENTION

"Process for the preparation of Gabapentin-Form-II"

320/MAS/2002
21-4-02

2. a) Matrix Laboratories Ltd, with its registered office at b)1-1-151/1, IV Floor, Sairam Towers, Alexander Road, Secunderabad, 500003, A.P, India c) an Indian Company

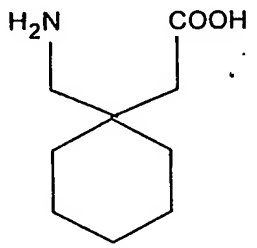
The following specification particularly describes the nature of the invention and the manner in which it is to be performed.

Field of the Invention:

The present invention relates to a new industrially feasible process for the direct preparation of Gabapentin Form-II without the formation of Form- III.via the Gabapentin acid addition salt to yield product that is substantially lactam free and very low content of chloride ions.

Background of the Invention:

Gabapentin, namely 1-aminomethyl-1-cyclohexaneacetic acids, of the Formula-1



Formula-1

Gabapentin is the active ingredient used for the treatment of various cerebral diseases like epilepsy, hypokinesia including fainting and other brain trauma and in general, it is deemed to produce an improvement in the cerebral functions.

Gabapentin and several processes for its preparation as the Hydrochloride salt, sodium salts are disclosed in US Patent Nos. US 4,024,175 and US 4,087,544.

All processes described in the prior art e.g. in US Patent Application No. US 2003/ 0009055, US 6,465,689, US 5,091,567, PCT publications WO 02/ 44,123, WO 02/ 34,709, WO 00/ 01,660, WO 99 / 14,184 and European patent EP 1,174,418, yields Gabapentin hydrochloride which is converted to the corresponding free amino acid by neutralization with a basic ion-exchanger followed by crystallization. US 4,894,476 specifically discloses a method for converting the hydrochloride salt into a crystalline monohydrate by eluting the aqueous solution through a basic ion-exchange resin, producing a slurry from the elute, adding an alcohol to the slurry and isolating by centrifuging and drying.

Alternate methods disclosed in US Patents US 5,132,451, US 5,095,148, US 5,091,567 and US 5,068,413 involve hydrogenation of the cyano intermediate to liberate the free amino acid.

PCT publication No. WO 98/ 28255 discloses a method for the conversion of hydrochloride salt into Gabapentin Form-II via Gabapentin Form-III by elaborate multistep procedure of dissolution into a solvent, filtration of inorganics, distillation of solvent under vacuum in a heating bath at temperature below 35°C, then adding a second solvent, and neutralizing with a base at 25°C to yield Form–III. Form-III is then converted to Form-II by slurrying in methanol at 25°C for 14 hrs or recrystallising it from methanol.

These processes are not industrially appropriate as large volumes of ion exchange columns and distillation of water are involved thereby leading to the formation of undesired lactam impurity. The method of conversion of hydrochloride into Form-II disclosed in PCT publication No WO-98/ 28255 involves the distillation of first solvent under vacuum at temperatures below 35°C, then addition of a second solvent for crystallization of Form-III and finally an extra step for the conversion of Form-III to required Form-II by slurring in methanol thereby lowering the yields, and producing a product with unacceptable levels of chloride ions and enhancing the cost of the final product.

In view of all the problems still there is a requirement of an industrial feasible process for preparation of Gabapentin Form-II with substantially lactam free and very low content of chloride ions.

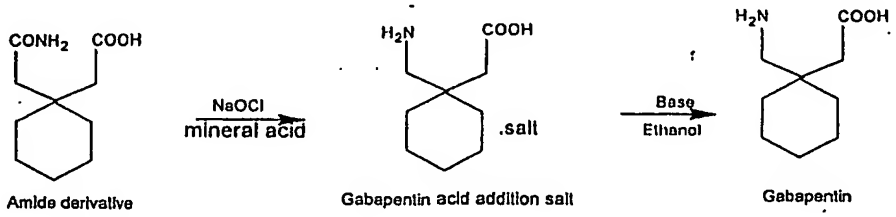
Summary of the invention:

The present invention relates to a new industrial feasible process for the preparation of Gabapentin by converting the Gabapentin acid addition salts directly to Form-II without the formation of Form- III.

Another object of the invention is to provide a process for the preparation of Gabapentin Form - II free from chloride ions and lactam impurity.

The present invention overcomes the disadvantages associated with prior art methods, by neutralizing the Gabapentin acid addition salts with a base at higher temperatures followed by cooling.

Accordingly, the present invention relates to a method for the preparation of Gabapentin by reacting 1,1-cyclohexane diacetic acid monoamide in the presence of alkali hypo halite followed by acidification with mineral acid in presence of an organic solvent to extract the liberated acid addition salt into that solvent. An ante solvent is added to crystallize the Gabapentin acid addition salt. The separated salt is then, suspending in organic solvent and neutralizing with a base at a specified temperature range, cooled to ambient temperature, followed by separation of Gabapentin Form-II, which is further purified by slurring in ethanol.



Amide derivative — Gabapentin acid addition salt — Gabapentin

Crude Gabapentin and the pure Gabapentin precipitated are in the polymorph Form-II and are anhydrous. With the crystalline structure from the coincidence of the IR spectrum and X-ray diffraction pattern of those of the said conventional product.

Further objectives and advantages of the present invention will be apparent from the detailed description of the disclosed invention to those skilled in the art.

Brief description of the drawings:

Fig. 1 is the X-ray diffraction pattern of the Gabapentin Form-II

Fig. 2 is the FTIR spectrum of the Gabapentin Form –II

Fig. 3 is the X-ray diffraction pattern of the Gabapentin Form-III

Fig.4 is the FTIR spectrum of the Gabapentin Form-III

Table 1.FTIR peaks of Gabapentin hydrate, Form-II and Form-III

S.No	Hydrate	Form-II	Form-III
1	1664		1664
2	1624	1615	1586
3		1546	1510
4	1542	1476	1460
5		1420	1420
6		1400	1402
7		1337	1333
8		1327	1,311
9	1292	1300	1290
10	1175	1165	1180
11	1154	1,133	1160
12	968	1120	1115
13		976	974
14	926	928	945
15	880	922	926
16	726	890	885
17	648	749	760

XRD peaks and 2 theta values

S.No	Hydrate	Form - II	Form- III
1	6.1	7.8	6.1
2	12.2	13.3	12.1
3	16	14.9	16.9
4	18.3	16.6	17.6
5	19.1	16.8	18.1
6	19.8	19.5	19.9
7	20.7	20.2	20.8
8	24.5	21.3	24.4
9	26.4	21.8	25.1
10	28.4	23	28.8
11	30.7	23.5	30.2
12	32.3	25.7	30.7
13		26.9	31.5
14		28	

Detailed description of the Invention:

The process of the present invention comprises::

- Reaction of 1,1-Cyclohexane diacetic acid mono amide with alkali hypohalite solution, acidification with mineral acid in presence of a solvent
- Extraction of the formed acid addition salt into organic layer
- Separation of the organic layer, drying over dehydrating agents
- Addition of an ante solvent, cooling to precipitate the acid addition salt and its isolation
- Dissolution of acid addition salt in a short chain alcohol
- Filtration of the solution to remove the insoluble materials
- Neutralization of the filtrate with a base at specified temperature range to liberate the free amino acid
- Separation of the liberated free amino acid by cooling, leaving the formed byproduct base-salt in the mother liquor / solvent
- Separation of the formed Gabapentin Form-II
- Purification of the product by slurring in ethanol in a specified temperature range
- Isolation of the product followed by drying

The Gabapentin acid addition salts are Gabapentin hydrochloride and Gabapentin hemisulphate hemihydrate.

The precipitated Gabapentin and the purified Gabapentin are identified and confirmed as polymorph Form-II with the XRD and IR data.

The 1,1-cyclohexane diacetic acid mono amide used as starting material is prepared as per the literature (US Patent No. 4,024,175).

For the reaction of 1,1-cyclohexane diacetic acid mono amide with alkali hypo halite, the preferred alkali hypo halite is sodium hypo chlorite solution and the reaction is carried out in the temperature range of about -10^0C to about 5^0C, with the preferred range is

about -5^0C to about 5^0C. Acidification of the reaction mass to a pH of about 2.0 and preferably below 2.0 in the range of about 1.0 to about 1.5 is carried out with mineral acid, the preferred mineral acids are Hydrochloric acid and Sulphuric acid in presence of an organic solvent in a temperature range of about 15^0C to about 25^0C. The preferred solvent is n-Butanol.

The reaction mass is allowed to settle and the organic layer is separated. The aqueous layer is extracted a few times with the organic solvent. The combined extracts is dried over dehydrating agents selected from anhydrous sodium sulphate, anhydrous magnesium sulphate and anhydrous calcium sulphate the preferred ones being anhydrous sodium sulphate or anhydrous magnesium sulphate.

The dried organic layer is treated with ante solvent, cooled if required to precipitate the acid addition salt. The ante solvent is selected from the hydrocarbons, aromatic hydrocarbons, alkyl ketones, alkyl ethers, the preferred solvent being hexane, toluene, acetone, di isopropyl ether or their mixtures.

The precipitated acid addition salt is separated by conventional methods such as filtration, centrifugation and dried to constant weight.

The Gabapentin acid addition salt is dissolved in short chain alcohols, preferred alcohol being ethanol, n-butanol at about 30^0C to about 35^0C, filtered to remove the insolubles, and then raising the temperature of the filtrate to about 70^0C preferably from 65^0C to 75^0C, slowly neutralized with an organic base. The preferred bases are tri ethyl amine and di isopropyl ethyl amine, maintain the reaction mass for 1 – 2 hrs at the temperature about 70^0C in the preferable range of about 65^0C to about 75^0C, cooling the mass gradually to about 10^0C to about 25^0C, preferably about 20^0C to about 25^0C, stirring for 1 to 2hrs followed by the separation of the precipitated free amine, washing of the wet cake with solvent such as ethanol and drying the product at temperature preferably between 45^0C to 50^0C.

Gabapentin is further purified by suspending in ethanol, raising the temperature to 60^0C to 70^0C, maintaining the suspension at this temperature for about one hour followed by gradual cooling and stirring for about 1 –2 hrs at temperature 20^0C – 25^0C. The purified product so formed is isolated and dried to obtain Gabapentin with chloride ions, sulphate ions in the pharmaceutically acceptable range of below 100 ppm and lactam impurity below 0.1%.

The invention can be further illustrated by a few non-limiting examples.

EXAMPLE - I

Stage – 1: Preparation of Gabapentin hemisulphate hemihydrate.

Sodium hypochlorite solution (6.25%, 625 gms) is cooled to 10^0C and sodium hydroxide flakes (51 gms) is dissolved in it by stirring for 10-15 min at 10^0C – 15^0C. The mass is further cooled to -5^0C. In a separate flask 1,1-cyclohexane diacetic acid monoamide (100 gms) is dissolved in 4N sodium hydroxide solution (150 ml) at 15^0C – 20^0C. The amide solution is slowly added to sodium hypochlorite solution at temperature -5^0C to -3^0C over 3hrs. And then maintained at about 0^0C for 2 hrs. The temperature is then slowly raised to 20 – 25^0C over 3 hrs and maintained for 4 hrs at 20^0C – 25^0C. Sodium metabisulphite solution (5 gms in 10 ml water) is then added. The reaction mass is filtered to remove any undissolved material. pH of the filtrate is adjusted to 9.0 by the addition of 1:1 dilute sulphuric acid at temperature 20^0C –25^0C. n-Butanol (200 ml) is added and the pH id further adjusted to 1.5 with sulphuric acid. The reaction mass is stirred for 10 – 15 min. and then allowed to settle. The layers are separated. The aq. layer is extracted with n-butanol (200 ml). The combined extract is dried over anhydrous sodium sulphate (15 gms). Di isopropyl ether (1200 ml) is slowly added at room temperature over 30 – 45 min to the dried extracted layer. The reaction mass is stirred for 1 hr and then cooled to 5^0C and stirred for 1 hr at 0 – 5^0C. The product is filtered, washed with di isopropyl ether (50 ml) and dried at 45^0C – 50^0C to constant weight.

Dry wt of Gabapentin hemisulphate hemihydrtae is 85 gms (Yield: 73.8%).

Chemical analysis of the hemisulphate hemihydrate is as follows:

a) Moisture content: 3.95% b) Sulphate content: 21.41%

Stage – 2: Conversion of Gabapentin hemisulphate hemihydrate to Gabapentin Form-II

The Gabapentin hemisulphate hemihydrate salt (100 gms) prepared as above in stage-1 is suspended in ethanol (700 ml) and stirred for 30 min. at room temperature. The insolubles is filtered and washed with ethanol (50 ml). The filtrate is heated to 70^0C – 75^0C and the pH of the filtrate is adjusted between 7.1 to 7.2 by slow addition of di isopropyl ethylamine solution (106 gm in 145 ml ethanol) at 70^0C - 75^0C over 1hr. The reaction mass is maintained for 2 hrs at 70^0C - 75^0C and then gradually cooled to 20^0C – 25^0C and maintained for about 1 hr. The filtered product is washed with ethanol (50 ml) and dried at 45^0C – 50^0C to constant weight.

Dry wt of the Gabapentin is 50 gms (Yield: 67%).

Stage –3: Purification of Gabapentin Form-II

The Gabapentin (50 gms) prepared as above is suspended in ethanol (300 ml) and the temperature is raised to 65^0C and maintained for 30 min. between 60^0C –65^0C. The mass is cooled to room temperature and stirred for 30min. at room temperature. The filtered product is washed with ethanol (25 ml) and dried at 50^0C – 55^0C to constant weight.

The dry weight of the Gabapentin Form-II is 45 gms (Yield: 90%)

The XRD and IR data is matched with the standard data available for the Form- II

EXAMPLE - 2

Stage – 1: Preparation of Gabapentin hydrochloride.

Sodium hydroxide (51 gms) is dissolved in sodium hypochlorite solution (6.25%, 625 gms) cooled to 10^0C. The solution is stirred for 10 – 15 min. And further cooled to -5^0C. In a separate flask 1,1-cyclohexane diacetic acid monoamide (100 gms) is dissolved in 4N sodium hydroxide solution (150 ml) at 15^0C – 20^0C. The amide solution is slowly added to the sodium hypochlorite solution at temperature -5^0C to -3^0C over 3hrs. The solution is then maintained at about 0^0C for 2 hrs. The temperature is gradually raised over 3 hrs to 20^0C – 25^0C and then maintained at this temperature for 4 hrs. Sodium

meta bisulphite solution (5 gms in 10 ml water) is then added to the solution. The reaction mass is filtered remove any undissolved material. pH of the filtrate is adjusted to around 9.0 by the addition of hydrochloric acid at temperature 20 – 25^{0}C. n-Butanol (200 ml) is added and the pH is further adjusted to 1.5 with hydrochloric acid and stirred for 10 – 15 min. The reaction mass is allowed to settle and layers are separated. The aq. layer is extracted with n-butanol (200 ml). The organic is dried over anhydrous sodium sulphate (15 gms). Di isopropyl ether (1200 ml) is slowly added to the dried organic layer at RT over 30 – 45 min and maintained for about 1 hr under stirring. The system is cooled to 5^{0}C and stirred for 1 hr at 0^{0}C – 5^{0}C.

The product is filtered, washed with di iso propyl ether (50 ml) and dried at 45^{0}C – 50^{0}C to constant weight and finally crystallized from tert.butanol – diisopropyl ether to get the pure Gabapentin hydrochloride.

Dry wt of the Gabapentin hydrochloride is 80.0 gms (Yield: 75.0%)

Stage – 2: Conversion of Gabapentin hydrochloride to Gabapentin Form-II

The Gabapentin hydrochloride salt (100 gms) prepared as above in stage-1 is suspended in ethanol (950 ml) and stirred for 30 min. at room temp. The insolubles are filtered and washed with ethanol (50 ml). The filtrate is heated to 70^{0}C – 75^{0}C and the pH is adjusted to 7.1 to 7.2 by slow addition of di isopropyl ethylamine solution (170 ml in 170 ml of ethanol) at 70 - 75^{0}C over 60 min. The reaction mass is maintained at 70^{0}C - 75^{0}C for 2 hrs, gradually cooled and maintained at 20^{0}C – 25^{0}C for about 1 hr. The product is filtered, washed with ethanol (50 ml) and dried at 45^{0}C – 50^{0}C to constant weight.

Dry wt of the Gabapentin Form-II is 52.8 gms (Yield: 66%).

Stage –3: Purification of Gabapentin Form-II

Gabapentin (50 gms) prepared as above is suspended in ethanol (350 ml) and the temperature is raised to 65^{0}C and maintained for 30 min. at 65^{0}C – 68^{0}C. The reaction mass is cooled to room temp and stirred for 30 min. The product is filtered, washed with ethanol (25 ml) and dried at 50^{0}C – 55^{0}C to constant weight.

The dry weight of the Gabapentin Form-II is 45 gms (Yield: 90%)

Claims:

We claim

1. A process for the direct preparation of Gabapentin Form-II without the formation of Form- III.via the Gabapentin acid addition salt in reaction steps comprising :
   - Reaction of the 1,1-cyclohexane di acetic acid mono amide with alkali hypo halite solution at temperature of about -10^0C to 5^0C, followed by acidification with mineral acid in presence of an organic solvent -1
   - Extraction of the formed acid addition salt with organic solvent - 2
   - Separation of the organic layer, drying over dehydrating agents
   - Addition of an ante solvent to precipitate the acid addition salt followed by its isolation
   - Dissolution of the acid addition salt in a short chain alcohol
   - Separation of the insolubles if any
   - Neutralization of the filtrate with base at temperature of about 70^0C to liberate the free amino acid
   - Isolation of the liberated free amino acid by cooling, leaving the formed by-product base-salt in the mother liquor / solvent
   - Separation of the formed Gabapentin Form-II
   - Purification of the product by slurring in ethanol at temperature of 60^0C-70^0C
   - Isolation of the final product by filtration followed by drying

   to yield Gabapentin Form-II that is substantially lactam free and sulphate ions less than 100 ppm and chloride ions less than 100 ppm with respect to Gabapentin

2. A process as claimed in claim 1, wherein acidification to pH 1.0 to 1.5 is carried out using sulphuric acid or hydrochloric acid

3. A process as claimed in claim 1, wherein the organic solvent - 1 is n-Butanol or MIBK or methylethyl ketone or THF, the preferred solvent being n-Butanol

4. A process as claimed in claim 1, wherein the organic solvent – 2 for extraction of acid addition salt is n-Butanol or MIBK or methylethyl ketone or THF, the preferred solvent being n-Butanol

5. A process as claimed in claim 1, wherein drying of organic layer is carried out over dehydrating agents such as anhydrous sodium sulphate and anhydrous magnesium sulphate and anhydrous calcium sulphate the preferred ones being anhydrous sodium sulphate or anhydrous magnesium sulphate

6. A process as claimed in claim 1, wherein the ante solvent is selected from Acetone or Toluene or n-Hexane or Di isopropyl ether

7. A process as claimed in claim 1, wherein the short chain alcohol is Ethanol or n-Butanol

8. A process as claimed in claim 1, wherein the base is selected from Di isopropyl ethylamine or Triethylamine

9. A process as claimed in claim 1, wherein the neutralization temperature is 65^0C-75^0C

Dated: 21-04-2003

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Abstract:

The present invention relates to a new industrial feasible process for the preparation of Gabapentin Form-II via Gabapentin acid addition salts with out forming Gabapentin Form-III that is substantially lactam free, sulphate ions less than 100 ppm and chloride ions less than 100 ppm with respect to Gabapentin.

330/MAS/2003

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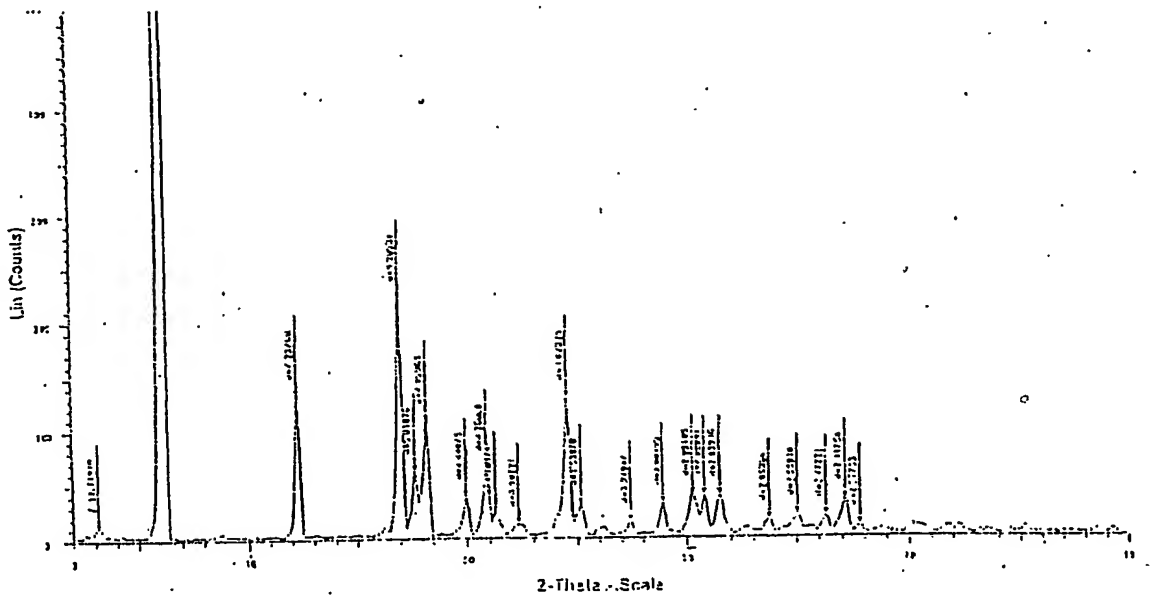

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6.122	14.42534	100.0
12.219	7.23766	8.2
17.020	5.20529	13.8
17.560	5.01826	3.8
18.203	4.86962	6.8
19.942	4.44875	2.3
20.832	4.26068	4.0
21.214	4.18474	1.4
22.306	3.98227	0.8
24.549	3.62325	8.1
25.145	3.53878	1.9
27.428	3.24917	0.9
28.948	3.08195	1.9
30.262	2.95105	2.4
30.814	2.89941	2.4
31.481	2.83946	2.4
33.749	2.65366	1.0
35.032	2.55938	1.2
36.309	2.47221	1.2
37.160	2.41758	2.1
37.812	2.37733	0.6

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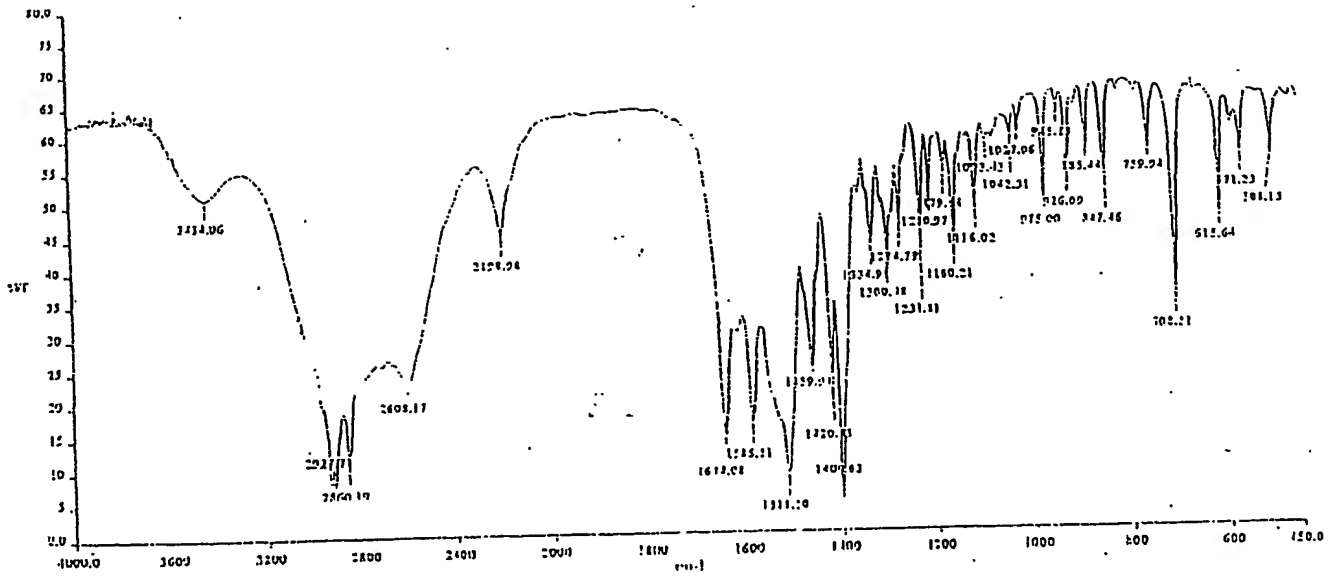

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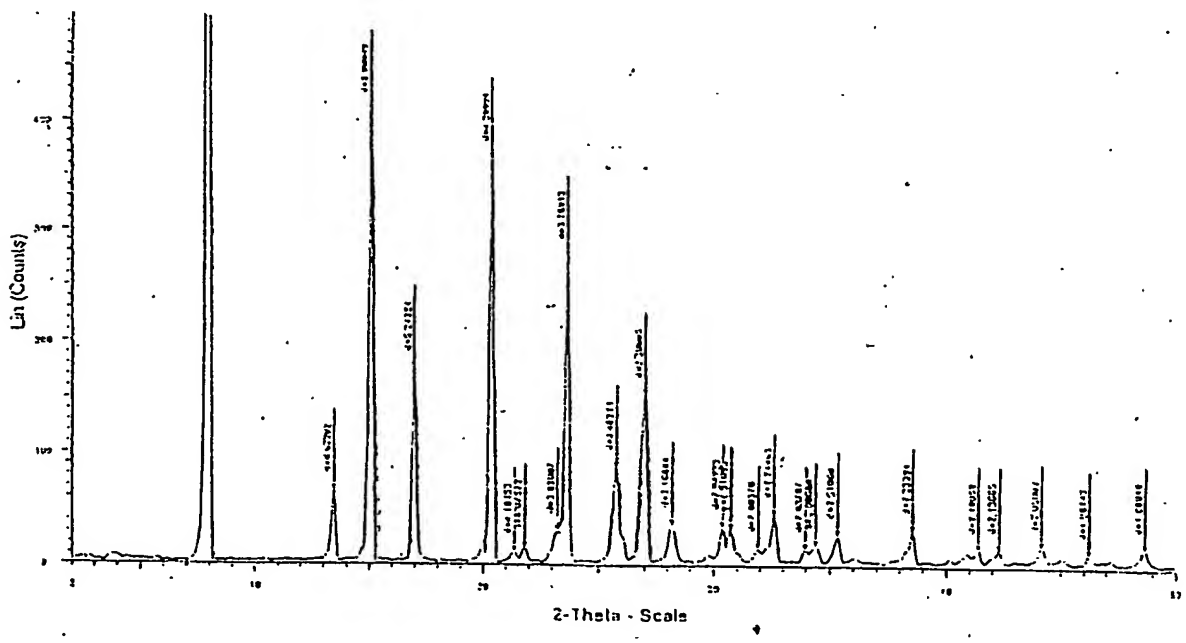

Single 2-Theta °	d value Angstrom	Intensity %
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15.003	5.90049	40.7
16.898	5.24254	17.4
20.305	4.36994	36.4
21.334	4.16153	1.1
21.789	4.07572	1.5
23.200	3.83087	3.0
23.585	3.76913	27.5
25.711	3.46211	8.6
26.947	3.30605	15.1
28.155	3.16688	3.6
30.355	2.94223	3.4
30.689	2.91095	3.2
31.893	2.80370	1.5
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35.299	2.54060	2.7
38.543	2.33394	3.1
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42.264	2.13665	1.5
44.142	2.05002	1.8
46.248	1.96143	1.1
48.666	1.86948	1.7

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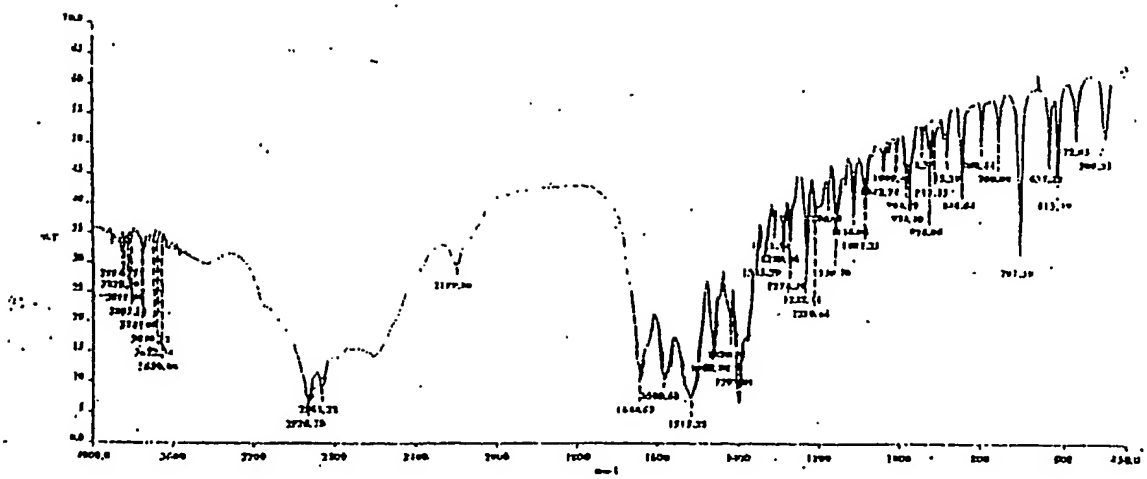

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